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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,827	08/06/2003	Manfred Schudok	2481.1762-01	6761

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ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,827	SCHUDOK ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II, claims 1-9, namely compound of formula I wherein in formula II, one of X^1 or X^2 is nitrogen and the other carbon namely isomeric pyridines, composition and method of use, in Paper file on 1/27/2005 is acknowledged.

Claims 1-9 will be examined to the extent the embrace the elected group II.

The traversal is on the ground(s) that the restriction requirement is improper based on MPEP§ 803.02 and relevant case law. This is not found persuasive for the following reasons.

First of all, the restriction is same as made in the parent application 09/965,790. A three-way restriction was made based on X^1 and X^2 in A of formula II and applicants elected Group III wherein X^1 and X^2 were both carbon. Upon making the restriction Final, and subsequent examination and prosecution, the application with elected invention had resulted in issuance of U S Patent 6,645,992. Instant claims, which are now subjected to two-way restriction, clearly excludes the choice of compounds of formula I when X^1 and X^2 are both carbon. Hence, three inventions provide in the three–way restriction made in the previous office action are distinct and independent is well settled.

Secondly, according to MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent or distinct as claimed and

(B) There must be a serious burden on the examiner if restriction is required.

As noted in the previous office action, they are directed to dissimilar compounds with varying cores such pyridazine vs pyridine vs cores. Group I and II require mutually exclusive search if a thorough search is intended. Classification of Group I is controlled by pyridazine core not the pyridine or benzoenoid core and hence searching in elected Group III, class 564/155 and /or 514/617 would not lead to compounds not having a pyridazine as required for Group I or Group II compounds bearing pyridine ring. Each class/subclass has to be searched in East or West. It is mandatory. There is serious search burden as several classes and subclasses are to be searched.

Applicants have not submitted evidence or identified such evidence now of record showing the core group to be obvious variants or clearly admitted on the record that all core groups embraced in the instant inventions are equivalent. In which case examiner needed not search all cores. A prior art which anticipates any one of the groups embraced by a specific core (i.e. choices of I or II) may then render the other core group an obvious variant. In other words, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In want of such assertion or evidence, searching the entire core would be serious search burden.

Applicants' also argue that the instant claims meet the substantial structural requirement and common utility requirement and therefore the restriction is not applicable. Again, this is not a persuasive as these criteria are applied in general to a 371 application of

PCT entering the national stage which require a special technical feature requiring unity of invention. Instant application is not a 371 of a PCT application.

In addition, the requirement for unity of invention is two-fold: (1) common utility and (2) sharing a substantial structural feature disclosed as being essential to the utility. Both these conditions are to be met with.

Applicants have not identified which is the substantial structural feature essential for the shared utility. They point to formula I for substantial structural requirement, which is the whole structure not the part bearing the substantial structural feature. Assuming that applicants intended the malonamide core, the four substituents A, B, R^1, R^2 are varible groups and the only no-variable core is CO-C-CO and there is no evidence in the specification or prior art that such a core contributes to the said utility. In fact the aryl and heteroaryl core bearing the amidine group appears to be essential for the said activity.

Therefore, the criteria that substantial structural feature disclosed as being essential to the utility is not met with.

In addition, the common utility requirement is also met with as evident from claims 5-9, which recite several distinct utilities.

Thus, both the above conditions for unity of invention are not met with.

In summary, the restriction requirement clearly meets MPEP § 803.02 and Case Law requirements.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-9 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 8/6/2003, are made of record.

Specification

First line of specification needs to be amended to indicate this application is a divisional application of 09/965,790, filed 10/01/2001, now US Patent 6,645,992.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim and share the same indefiniteness

1. Claims 1 and 2 are indefinite as they recite the phrase "derivative" which implies more than what is being positively recited therein. Particularly, note the term derivative can include any organic compound bearing the core structure and hence the metes and bounds of the claim remain unknown. Its replacement with "compound" is suggested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting blood clotting, thromboembolic disease, restenosis or inflammatory response, does not reasonably provide treating all or any cardiovascular disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

The instant claims are drawn to "treating cardiovascular disorders" in patient. The scope of the claim as recited includes all or any disorders including those yet to be discovered as due to thrombosis. As recited claim language includes disorders, which may not be related to the instant mode of action. The instant compounds are disclosed to have factor VIIa inhibitory activity which relates to inhibition of thrombin. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating cardiovascular disorders' solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (PubMed Abstract enclosed) wherein with regards to antithrombotic therapies, it is stated "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (PubMed Abstract enclosed) with regards to therapeutic approach of thromboembolic disorders, expresses

that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating all or any cardiovascular disorders even those yet to be discovered as related to Factor VII a activity and even that does not require factor VIIa inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all cardiovascular disorders with the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show preventive effect thrombotic condition and the state of the art is that the effects of thrombin inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace not only treatment Factor VIIa activity related disorders but also those which are not related to the Factor VIIa inhibiting activity of instant compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards 'treating' the variety of cardiovascular disorders of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Allowable Subject Matter

Claims 1-6 and 8-9 would be allowable, barring any prior art finding in a subsequent search, if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and limiting the scope of the claims to elected subject matter. Said claims 1-6 and 8-9 would be allowed since compound, specific species, process of making, composition and method of use embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

Venkataraman Balasubramanian

4/14/2005